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Interventions for improving medication adherence in solid organ transplant recipients (Protocol)

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[Intervention Protocol]

Interventions for improving medication adherence in solid organ transplant recipients

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

This review aims to look at the benefits and harms of using interventions for improving adherence to immunosuppressant therapies in solid organ transplant recipients, including paediatric and adult heart, lung, kidney, liver and pancreas transplant recipients.

BACKGROUND

Description of the condition

Solid organ transplantation refers to transplantation of the heart, lungs, kidney, liver or pancreas from a cadaveric or living donor (Linden 2009). Solid organ transplantation is regarded as a highly successful form of intervention following irreversible organ failure, with transplant success rates varying across organ types and age of recipient. One-year graft survival for an adult kidney transplant recipient is estimated as 92.4% for a deceased donor and 96.3 for a living donor. In paediatric (0 to 18 years) kidney transplant recipients, graft survival is estimated as 91.5% for deceased donors and 96.4% for living donors (ERA-EDTA 2015). For heart transplant, one-year graft survival is estimated at 13 years (Lund 2016), and 15.7 to 21.5 years for paediatric recipients (Rossano 2016). For lung transplant, one-year graft survival is estimated as 8 years for adults (Yusen 2016) and 5.4 years for paediatric recipients (Goldfarb 2016). For liver, one-year graft survival is estimated as 79% for adults, and 84% for children > 2 years of age (Adam 2003). One-year graft survival for pancreas transplant is estimated as 78% for adults (Gruessner 2011), with long-term graft survival estimated as 9.6 years for paediatric recipients (Spaggiari 2017). Adequate suppression of the immune system is required for short- and long-term survival of the organ transplant, thus adherence to immunosuppressive therapy forms the central part of prevention of organ rejection, graft loss and mortality following an organ transplant. Immunosuppressive strategies and pharmacologi-

cal agents are consistent across all solid organ transplants, and most commonly involve lifelong oral administration of a calcineurin inhibitor and an antimetabolite, with or without corticosteroids, in order to sustain a graft free from rejection and minimise the potential for acute or chronic graft loss, or mortality following transplantation (Butler 2004; Posadas Salas 2014).

There remains a significant imbalance between organ availability and numbers listed for transplantation, with a shortage of organs for transplantation reported worldwide (Rudge 2012). The cost benefits of optimised post-transplant graft survival are substantial when considering the healthcare cost savings through long-term successful transplantation (Anyanwu 2002; Sagmeister 2002; Whiting 2004), as graft failure incurs significant hospitalisation costs, in addition to anti-rejection treatment and life-sustaining therapies. The importance of adhering to immunosuppressive therapy cannot be overemphasised, with the odds of organ failure increased seven-fold for non-adherent recipients versus adherent recipients (Butler 2004). This suggests that near-perfect adherence is essential for reduced patient morbidity and overall reduced healthcare costs (Low 2015). Medication adherence is defined as 'the extent to which a patient acts in accordance with the prescribed interval and dose of a medication regimen' (Cramer 2008). Accurate estimates of non-adherence are difficult to obtain, given variability in type of adherence assessment and study quality (Nieuwlaat 2014). Subjective measures including self-report assessments yield superior rates of adherence, however are open to considerable reporting biases (Moran 2017). In transplantation, objective measures of adherence using clinical parameters, such as pharmacy refill data, electronic measurement of pillbox use (Denhaerynck 2005), assay of medication or fluctuation in medication trough levels (O'Regan 2016), and/or clinical outcome are reported to yield the highest immunosuppressant non-adherence rates (Denhaerynck 2005; De Bleser 2009).

Meta-analyses of all solid organ transplant types reported a 22.6% non-adherence rate to immunosuppressant therapy. Rates of non-adherence varied by type of transplant, with highest rates observed for kidney transplants (36%), and lowest for liver transplant (6%) (Dew 2007). The rate of non-adherence may also vary by age of the transplant recipient, with a rate of non-adherence to immunosuppressants in paediatric recipients estimated as 6 cases per 100 person-years (Dew 2009).

Description of the intervention

Post-transplant immunosuppressant therapy involves a complex programme of medication adherence, including daily dosing schedules, monitoring and management (Posadas Salas 2014). Specific strategies to maintain clinically advised levels of adherence to immunosuppressants haven't been identified, and such strategies remain absent from treatment guidelines to date. Previous work in 2009, similar to this proposed review, focused on adherence to immunosuppressant therapies for kidney, heart and liver transplants and identified that interventions focusing on improving treatment adherence largely applied a combination of approaches to improve adherence, namely incorporating educational/cognitive, counselling/behavioural, or psychological/affective domains (De Bleser 2009). Method of intervention delivery varied widely across studies, including pharmacy, nursing and patient-led interventions. Authors concluded that limited improvements in adherence to immunosuppressants were evident, however no single type of intervention emerged as the most effective in improving adherence, and poor methodological quality was evident in 58% of studies identified. Such findings have been reported for other chronic and acute disease populations (Bangalore 2007; Nieuwlaat 2014).

It is becoming increasingly recognised that reliance on technology is an emerging strategy in healthcare for supporting patient-oriented self-management, and different interventional platforms and innovative technologies are being developed to improve adherence in chronic health conditions (Nieuwlaat 2014). Individually tailored medical mobile apps in particular show potential as an inexpensive and accessible method of intervention delivery to improve adherence to complex medication regimens (Dayer 2013). This proposed review provides an opportunity to identify and examine the efficacy of new innovative intervention platforms for improving adherence, in addition to more commonly identified intervention delivery platforms, such as tailoring educational materials, reinforcement, feedback, and behavioural skills training (Mullen 1992).

How the intervention might work

It is often assumed that the transplant recipient should be motivated by the potential benefits of successful transplantation to follow the prescribed immunosuppressant regimen, however estimated non-adherence rates question this assumption. In order to improve medication adherence, it is vital to first assess the behaviour accurately, and understand what is driving non-adherence. Reasons for general non-adherence to prescribed medications are multi-dimensional, and can be attributed as 'intentional' or 'non-intentional'. Intentional non-adherence involves conscious decision-making to alter or abstain from the prescribed regimen, whilst non-intentional non-adherence arises from forgetting, misunderstanding medication instructions or administering incorrect doses (DiMatteo 2012). Limited evidence is available for examination of reasons for non-adherence post-transplant, however factors such as psychosocial barriers in adult recipients, and lower family cohesion and child distress for paediatric recipients have been associated with poorer medication adherence post-transplant (Dew 2007; Dew 2009). Given the complexity of barriers to adherence, strategies to improve adherence must be capable of addressing the multi-dimensionality of medication adherence. Interventions which identify the reasons for the target behaviour (e.g. intentional versus non-intentional behaviour) and systematically develop in-

tervention components to address these behavioural drivers are likely to be more effective than interventions whereby a systematic, theory-driven approach is not applied (Davies 2010; Davis 2015: Michie 2011).

Why it is important to do this review

Adherence is the single most important modifiable factor that affects treatment outcome in chronic disease management. Consequently, identification of successful modes of intervention to improve adherence to immunosuppressant therapy is outlined as a research priority in kidney disease (Tong 2015). Given the reported high non-adherence rates, coupled with the critical importance of adherence to the immunosuppressant regimen to maximise and maintain successful transplantation, clear evidence is required to identify effective interventions which improve adherence after a solid organ transplant.

OBJECTIVES

This review aims to look at the benefits and harms of using interventions for improving adherence to immunosuppressant therapies in solid organ transplant recipients, including paediatric and adult heart, lung, kidney, liver and pancreas transplant recipients.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs), quasi-RCTs (RCTs where allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods), and cluster RCTs examining interventions to improve adherence following a solid organ transplant (heart, lung, kidney, liver, pancreas).

Types of participants

All solid organ transplant recipients, including adult and children.

Inclusion criteria

All solid organ transplant recipients, including first or subsequent transplant, and multi-organ transplants.

Exclusion criteria

Studies including populations without a solid organ transplant will be included only if the data for the solid organ transplant recipients can be analysed separately.

Types of interventions

Studies addressing interventions to improve adherence to immunosuppressant medication in comparison to a control arm will be included. Comparisons of interventions to usual routine care will also be included. Given the wide variation in types of interventions to address adherence, and methods of adherence measurement, interventions of any sort intended to affect adherence with prescribed, self-administered medications will be included, but not restricted to:·

- Patient educational interventions (e.g. books, leaflets, posters, videos, interactive modules)
- Pre-planned telephone contacts with nurses/medical team
- Electronic medication management interventions
- Pharmacy interventions
- Medical mobile apps
- Cognitive behavioural therapy/counselling/behavioural interventions
- Motivational interviewing
- Coaching/self-efficacy training
- Behavioural contracting
- A combination intervention including one or more of the above outlined strategies.

Types of outcome measures

Primary outcomes

Given the lack of a gold-standard method of assessing adherence to immunosuppressant medication, both subjective and objective surrogate measures of adherence will be included. Potential measures of adherence include, but are not restricted to:

1. Patient behaviours (e.g. self-reported adherence, pill count/electric monitoring devices);
2. Clinical parameters (e.g. calcineurin inhibitor (CNI) levels, CNI level variability, pharmacy reconciliation, absolute lymphocyte count, clinically assessed organ rejection, biopsy-proven organ rejection).

Secondary outcomes

1. Organ rejection
2. All-cause mortality
3. Non-fatal events
4. Adherence to other prescribed medications
5. Health service usage (e.g. clinical attendance, hospitalisations)

6. Health-related quality of life.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Kidney and Transplant Specialised Register through contact with the Information Specialist using search terms relevant to this review. The Cochrane Kidney and Transplant Specialised Register contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about Cochrane Kidney and Transplant.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described will be used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts will be screened independently by two authors, who will discard studies that are not applicable; however studies and reviews that might include relevant data or information on studies will be retained initially. Two authors will independently assess retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria. Disagreements between authors in the screening process will be resolved by inclusion of a third reviewer.

Data extraction and management

Data extraction will be carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals will be translated before assessment. Where more than one publication of one study exists, reports will be grouped together and the publications that include data relating to relevant outcomes will be used in the analyses. Where relevant outcomes are only published in earlier versions these data will be used. Any discrepancy between published versions will be highlighted. Differences between authors will be reconciled by discussion with of a third author.

Assessment of risk of bias in included studies

The following items will be independently assessed by two authors using the risk of bias assessment tool Higgins 2011 (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
    - Participants and personnel (performance bias)
    - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (e.g. organ rejection, death) results will be expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment (e.g. rate of adherence, biochemical indices of adherence to immunosuppressants, quality of life measures), the mean difference (MD) will be used, or the standardised mean difference (SMD) if different scales have been used.

Unit of analysis issues

If designs other than parallel designs are identified, study attributes will be taken into consideration during analysis, e.g. if a cluster design or cross-over RCT is identified.

Dealing with missing data

Any further information required from the original author will be requested by written correspondence (e.g. emailing corresponding author) and any relevant information obtained in this manner will be included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population will be carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals will be investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) will be critically appraised Higgins 2011.

Assessment of heterogeneity

We will first assess the heterogeneity by visual inspection of the forest plot. We will quantify statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of I^2 values will be as follows.

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi² test, or a confidence interval for I^2) (Higgins 2011).

Assessment of reporting biases

If possible, funnel plots will be used to assess for the potential existence of small study bias Higgins 2011.

Data synthesis

Data will be pooled using the random-effects model but the fixed-effect model will also be used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be used to explore possible sources of heterogeneity. Heterogeneity among participants could be related to age or other participant characteristics, intervention type, method of adherence assessment. Adverse effects will be tabulated and assessed with descriptive techniques, as they are likely to be different for the various agents used. Where possible, the risk difference with 95% CI will be calculated for each adverse effect, either compared to no treatment or to another agent. The following subgroup analyses are proposed:

1. Age (e.g. ≤ 13; 14 to 18; 19 to 40; 41 to 65; > 65)
2. Type of organ transplant (e.g. heart, lung, kidney, liver, or pancreas)
3. First versus subsequent transplant
4. Acute rejection phase versus long-term post-transplant phase (0 to 6 months; ≥ 6 months to 12 months, > 12 months)
5. Objective versus subjective adherence
6. Intervention type (e.g. counselling/educational versus other; brief versus intensive; Health Care Professional (HCP) contact versus non-HCP contact).

Further exploratory analyses will be undertaken for clinically relevant factors related to specific transplant type (e.g. alcohol and/or drug use for liver transplant, smoking status for lung transplant).

Sensitivity analysis

We will perform sensitivity analyses in order to explore the influence of the following factors on effect size.

1. Repeating the analysis excluding unpublished studies
2. Repeating the analysis taking account of risk of bias, assessed by co-authors using the Cochrane Risk of Bias tool
3. Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
4. Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country
5. Repeating the analysis excluding studies with an attrition rate of over 30%, or where differences in attrition between groups exceed 10%, or both
6. Repeating the analysis excluding cluster-randomised studies
7. Repeating the analysis taking account of study design (cross-sectional versus inception cohort).

'Summary of findings' tables

We will present the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). We plan to present the following outcomes in the 'Summary of findings' tables.

- Adherence to immunosuppressant medication
- Organ rejection
- All-cause mortality
- Non-fatal events
- Adherence to other prescribed medications
- Health service usage (e.g. clinical attendance, hospitalisations)
- Health-related quality of life.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Organ Transplantation] this term only 2. MeSH descriptor: [Lung Transplantation] explode all trees 3. MeSH descriptor: [Heart Transplantation] explode all trees 4. MeSH descriptor: [Liver Transplantation] this term only 5. MeSH descriptor: [Kidney Transplantation] this term only 6. MeSH descriptor: [Pancreas Transplantation] this term only 7. pancreas transplant*:ti,ab,kw (Word variations have been searched) 8. kidney transplant*:ti,ab,kw (Word variations have been searched) 9. lung transplant*:ti,ab,kw (Word variations have been searched) 10. heart transplant*:ti,ab,kw (Word variations have been searched) 11. liver transplant*:ti,ab,kw (Word variations have been searched) 12. solid organ transplant*:ti,ab,kw (Word variations have been searched) 13. spk:ti,ab,kw (Word variations have been searched) 14. {or #1-#13} 15. MeSH descriptor: [Patient Compliance] this term only 16. MeSH descriptor: [Medication Adherence] this term only 17. MeSH descriptor: [Treatment Refusal] explode all trees 18. MeSH descriptor: [Patient Education as Topic] explode all trees 19. medication adherence:ti,ab,kw (Word variations have been searched) 20. medication compliance:ti,ab,kw (Word variations have been searched) 21. patient compliance:ti,ab,kw (Word variations have been searched) 22. patient adherence:ti,ab,kw (Word variations have been searched) 23. treatment refusal:ti,ab,kw (Word variations have been searched) 24. {or #15-#23} 25. {and #14, #24

(*Continued*)

MEDLINE	1. Organ Transplantation/ 2. Kidney Transplantation/ 3. Pancreas Transplantation/ 4. exp Lung Transplantation/ 5. exp Heart Transplantation/ 6. Liver Transplantation/ 7. (pancreas$ transplant$ and kidney$ transplant$).tw. 8. spk.tw. 9. lung transplant$.tw. 10. heart transplant$.tw. 11. liver transplant$.tw. 12. solid organ transplant$.tw. 13. kidney transplant$.tw. 14. pancreas transplant$.tw. 15. or/1-14 16. Patient Compliance/ 17. Medication Adherence/ 18. Treatment Refusal/ 19. (medication$ and (adherence or compliance)).tw. 20. (patient$ and (complian$ or adherence)).tw. 21. treatment refusal.tw 22. Patient Education as Topic/ 23. or/16-22 24. and/15,23
EMBASE	1. organ transplantation/ 2. exp heart transplantation/ 3. exp kidney transplantation/ 4. exp liver transplantation/ 5. pancreas transplantation/ 6. exp lung transplantation/ 7. kidney pancreas transplantation/ 8. or/1-7 9. medication compliance/ 10. patient compliance/ 11. medication adherence.tw. 12. medication compliance.tw. 13. patient compliance.tw. 14. treatment refusal.tw 15. or/9-14 16. and/8,15

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random)
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention
	Unclear: Insufficient information about the sequence generation process to permit judgement
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear: Randomisation stated but no information on method used is available
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement

(*Continued*)

Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)

(*Continued*)

	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: LM
2. Study selection: LM, FD
3. Extract data from studies: LM, KW
4. Enter data into RevMan: LM
5. Carry out the analysis: LM, FD, KW, AH
6. Interpret the analysis: all authors
7. Draft the final review: all authors
8. Disagreement resolution: AH
9. Update the review: LM

DECLARATIONS OF INTEREST

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